Intralymphatic Immunotherapy With Autologous Semen in a Korean Man With Post-Orgasmic Illness Syndrome

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ABSTRACT

Post-orgasmic illness syndrome (POIS) is a very rare disease characterized by local allergic symptoms and transient flu-like illness that nearly always occur after masturbation, coitus, or spontaneous ejaculation and last for 2 to 7 days. In a previous case report, 2 patients with POIS received hyposensitization therapy composed of multiple subcutaneous injections of autologous semen that resulted in a gradual decrease of symptoms. However, this procedure requires patients to endure pain and discomfort during frequent subcutaneous injections and preceding masturbations to obtain the autologous semen used for therapy. Recent studies have suggested that intralymphatic immunotherapy is a promising new method of allergen-specific immunotherapy against allergic diseases, showing a faster onset and longer duration of therapeutic effects after only several intralymphatic injections. We report on a case of a Korean man with POIS who received intralymphatic immunotherapy that alleviated POIS-related symptoms and in whom the existence of semen-specific immunoglobulin E was confirmed using immunoglobulin E immunoblotting and enzyme-linked immunosorbent assay. **Kim TB, Shim YS, Lee, SM, et al. Intralymphatic Immunotherapy With Autologous Semen in a Korean Man With Post-Orgasmic Illness Syndrome. Sex Med 2018;6:174–179.**

Key Words: Post-Orgasmic illness; Injection; Intralymphatic; Desensitization; Immunologic; Semen

INTRODUCTION

Post-orgasmic illness syndrome (POIS) is a very rare disease characterized by local allergic symptoms and a transient flu-like illness that nearly always occur after ejaculation and last for 2 to 7 days.[1,2]

Waldinger and Schweitzer[1] 1st reported on 2 cases of POIS in 2002; that study summarized the characteristics of 45 POIS cases and subcutaneous immunotherapy (SCIT) with autologous semen was performed for 2 patients. This treatment led to a gradual decrease of complaints, resulting in 90% and 60% amelioration of POIS complaints at 15 and 31 months, respectively.[2,3] However, this procedure requires patients to endure pain and discomfort during frequent subcutaneous injections and preceding masturbations to obtain the autologous semen used for therapy.

Recently, intralymphatic immunotherapy (ILIT), a new method of allergen-specific immunotherapy (AIT) that requires only 3 to 6 injections into the inguinal lymph nodes at 4-week intervals, yielded symptom relief that occurred more rapidly than that associated with SCIT and lasted up to 3 years in patients with allergic rhinitis.[4–7]

We report on a case of a Korean man with POIS who received ILIT that alleviated his POIS-related symptoms and in whom the existence of semen-specific immunoglobulin (Ig) E was confirmed using IgE immunoblotting and enzyme-linked immunosorbent assay (ELISA).

CASE REPORT

A 30-year-old Korean man visited the university hospital complaining of flu-like symptoms that occurred after masturbation. He 1st masturbated 9 years previously and had various symptoms, including a sore throat, sputum, malaise, myalgia, arthralgia, rhinorrhea, sneezing, weakness, fatigue, fever, feverishness, chill, anorexia, residual urine sensation, voiding difficulty, weak urinary stream, postvoiding dribbling, depression,

Received August 12, 2017. Accepted December 14, 2017.

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https://doi.org/10.1016/j.esxm.2017.12.004

anxiety, and irritability, that nearly always occurred 3 to 4 hours after ejaculation and lasted for 48 hours with spontaneous regression. He was diagnosed with POIS, because his symptoms were consistent with the 5 diagnostic criteria.[1,2] He also had food allergies and complained of lip edema after ingestion of shrimp. Serum IgE level, which was measured using the ImmunoCAP system (ThermoFisher Scientific, Uppsala, Sweden), was 403 U/mL and levels of crab- and shrimp-specific IgE were 6.58 U/mL (class 3) and 20.0 U/mL (class 4), respectively. Prostate-specific antigen levels were normal (0.52 ng/mL). Serum total IgA, IgM, IgG, IgG1, IgG2, and IgG4 levels were within normal limits, whereas IgG3 was somewhat decreased (eTable 1). For sex hormones, estradiol was increased, prolactin and testosterone were decreased, and luteinizing hormone and follicle-stimulating hormone were within normal limits.

We proposed abstinence, scheduled masturbation during holidays, and prescription drugs, including non-steroidal anti-inflammatory, antihistamine, and mucolytic drugs, to relieve POIS-related symptoms. We also suggested SCIT or ILIT with autologous semen as a causative treatment against POIS and provided all references on POIS and ILIT with sufficient explanation and discussion. The patient eventually decided to undergo ILIT with autologous semen and provided informed consent.

We performed ILIT and evaluated POIS status before and 8 and 15 months after the 1st injection of ILIT (eFigure 1). Before ILIT, the patient was asked to score the severity of each POIS-related symptom using a visual analog scale ranging from 0 to 100 mm and to describe the duration of each. The patient also was asked to complete the Male Sexual Health Questionnaire (MSHQ) and was evaluated using the International Index of Erectile Function (IIEF).[8,9] The patient's semen and serum were obtained, and a skin prick test (SPT) and intradermal test with autologous semen were performed before and 8 months after the 1st ILIT injection.

Using ultrasound guidance and a 25-gauge needle, autologous semen was aseptically injected into an inguinal lymph node at a dilution of 1:40,000.[3] Then, the concentration was increased by 3-fold, as in a previous study of ILIT.[4,6] The patient complained of transient mild pain and a warm and abnormal sensation at the local injection site after each injection of ILIT. After the 3rd and 4th injections, the patient also complained of flu-like symptoms, including fatigue, chill, a burning sensation in the eyes, sore throat, and paratonsillar hypertrophy; these symptoms persisted for 3 to 4 weeks with an intensity that remained at 50% to 60% 5 days after the 3rd injection and at 60% to 70% 5 days after 4th injection. After sufficient discussion, the patient requested that he receive the 5th injection with the full concentration of autologous semen and stated that he did not want further injections thereafter. Based on this request, we performed the 5th injection with the full concentration of autologous semen as the last dose.

At 8 and 15 months after the 1st injection of ILIT, all POIS-related symptoms except sore throat and urinary symptoms were alleviated and their durations were shortened (Table 1). In particular, sneezing completely subsided. Moreover, the patient's responses to several questions on the MSHQ and IIEF indicated alleviation of discomfort after ejaculation and improvement in sexual function (eTable 2). His answers to other questions on the MSHQ or IIEF did not change after ILIT. Time from erection to ejaculation also remained unchanged at 5 minutes. According to the semen analysis, the amount of semen and sperm with normal motility and morphology increased 8 months after ILIT (eTable 3). Sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE) analysis of seminal fluid showed multiple protein bands with an apparent molecular mass ranging from 10 to 170 kD, as previously described[10] (eFigure 2). The IgE immunoblotting of autologous seminal fluid incubated with serum from the patient and 1 healthy control showed IgE binding bands at 14, 16, 34, and 55 kD (eFigure 3). The IgE binding band at 55 kD was particularly prominent before ILIT, but it was fainter when seminal fluid was incubated with serum obtained from the patient 8 months after ILIT. In addition, ELISA analysis showed that the level of semen-specific IgE was increased in the patient's serum before ILIT compared with the healthy control, but it had deceased to levels similar to those of the healthy control 8 months after ILIT (eFigure 4). Skin reactivity to the SPT and intradermal test with serially diluted autologous semen increased 8 months after ILIT (eTable 4).

The study was approved by our institutional review board.

DISCUSSION

Waldinger et al[2,3] hypothesized that allergies could play a role in POIS and examined the allergic history and measured serum levels of total IgE in all patients and performed hyposensitization therapy in 2 patients. Their hypothesis seems reasonable because most of their subjects (87%) developed POIS-related symptoms within 30 minutes of ejaculation, which suggests an immediate hypersensitive allergic reaction. In addition, some of their subjects (22%—44%) had ocular and nasal symptoms similar to those of allergic rhinoconjunctivitis. Interestingly, POIS-related symptoms were alleviated after SCIT in 2 subjects.[2,3] However, because most subjects with POIS frequently had flu-like symptoms, such as extreme fatigue, exhaustion, concentration difficulties, irritation, feverishness, extreme warmth, and perspiration, which are not typical allergic symptoms, the pathogenesis of POIS cannot be entirely explained by allergies. In addition, some but not all of their subjects had existing allergic dieases.[2] Furthermore, although SPT with autologous semen had a positive effect in most of their subjects who underwent SPT,[2] Jiang et al[10] suggested that even healthy controls showed positive SPT results with autologous semen, and no semen-specific IgE was detected in the serum of patients with POIS through SDS-PAGE, Western blotting, or ELISA. It is possible that not all patients with POIS have allergies and that multiple causes exist for this syndrome.

In contrast to the case report by Jiang et al,[10] we detected the existence of serum semen-specific IgE in our patient through SDS-PAGE, Western blotting, and ELISA. Moreover, our

Table 1. Severity and duration of symptoms related to post-orgasmic illness syndrome before and 8 and 15 months after intralymphatic immunotherapy

	Severity (VAS, mm)*	Duration (h)
Symptom	Baseline → 8 mo → 15 mo	Baseline → 8 mo → 15 mo
General		
Weakness	100 → 80 → 70	48 → 40 → 40
Fatigue	100 → 80 → 70	48 → 40 → 40
Fever	100 → 50 → 20	48 → 24 → 12
Feverishness	100 → 50 → 20	48 → 24 → 12
Chill	100 → 50 → 20	48 → 24 → 12
Malaise	100 → 80 → 60	48 → 48 → 48
Myalgia	100 → 80 → 60	48 → 48 → 48
Arthralgia	100 → 80 → 60	48 → 48 → 48
Ocular		
Burning sensation	100 → 60 → 60	48 → 36 → 40
Respiratory		
Rhinorrhea	100 → 60 → 60	48 → 36 → 36
Sneezing	100 → 60 → 0	48 → 36 → 0
Sore throat	60 → 60 → 60	48 → 48 → 48
Sputum	100 → 50 → 40	48 → 24 → 24
Gastrointestinal		
Anorexia	100 → 70 → 70	48 → 40 → 24
Urinary		
Residual urine sensation	80 → 80 → 80	48 → 48 → 48
Voiding difficulty	80 → 80 → 80	48 → 48 → 48
Weak stream	80 → 80 → 80	48 → 48 → 48
Dribbling	80 → 80 → 80	48 → 48 → 48
Neuropsychiatric		
Depression	100 → 80 → 50	48 → 40 → 24
Anxiety	100 → 50 → 40	48 → 24 → 20
Irritability	100 → 80 → 80	48 → 40 → 36

VAS = visual analog scale.
*The VAS ranged from 0 to 100 mm.

patient had POIS-related symptoms 3 to 4 hours after ejaculation and experienced the alleviation of most POIS-related symptoms after ILIT, which indicates that his POIS might be associated with an allergic type I hypersensitivity reaction. Sneezing, a typical symptom of allergic rhinitis, completely disappeared 15 months after ILIT, but the sore throat and urinary symptoms, including residual urine sensation, voiding difficulty, weak stream, and dribbling, remained unchanged after ILIT. We also observed lower levels of IgG3 in the patient's serum. Variable disorders of the innate and adaptive immune systems, including T-helper cell type 1, 2, and 17 immunity, might be involved in the pathogenesis of POIS, and the roles of specific components of the immune system remain to be investigated.

Hyposensitization therapy, or AIT, can have therapeutic effects in patients with POIS in whom allergies are a dominant etiologic factor. The present patient was judged to belong to this group of patients and received ILIT, which alleviated his POIS-related symptoms. The mechanism of ILIT is not sufficiently understood, but we propose that ILIT might be mediated by plasmablasts, plasma cells, and memory B cells that are activated by allergens injected into lymph nodes and produce allergen-specific IgE, IgG4, or other antibody isotypes with or without enhanced affinity.[7]

Waldinger et al[2] reported that 56% of their patients had lifelong premature ejaculation with an intravaginal ejaculation latency time shorter than 1 minute. However, none of their patients had erectile dysfunction according to the IIEF-5 criteria. The patient described by Jiang et al[10] had normal erectile function and sexual desire but also complained of premature ejaculation. In this case, the patient had erectile dysfunction and other sexual dysfunctions described by the IIEF and MSQH, all of which were alleviated after ILIT. However, time from penile erection to ejaculation remained at 5 minutes before and after ILIT.

Serum levels of estradiol were increased in the present patient and in the patient described by Jiang et al[10] (86.98 and 43.07 pg/mL, respectively), whereas serum levels of other sexual hormones were not consistent in the 2 studies. Additional studies are needed to determine the role of sex hormones in POIS.

Waldinger et al[2] also reported incoherent speech, concentration difficulties, easily irritable mood, photophobia, and depression in some patients, which is similar to symptoms of "opioid withdrawal syndrome."[10] The present patient also complained of irritability, anxiety, and depression that were partly alleviated after ILIT. However, the exact mechanisms underlying neuropsychiatric disorders and the effects of AIT on these disorders in patients with POIS remain unknown.

In conclusion, we performed ILIT in a Korean man with POIS. ILIT alleviated POIS-related symptoms and alleviated sexual dysfunction. However, this is a single case report, so we cannot exclude the possibility that the patient might have had spontaneous remission. More studies are needed to elucidate the pathogenesis, epidemiology, clinical manifestations, and diagnostic and therapeutic modalities for PIOS, including SCIT, ILIT, and other forms of AIT.

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Conflicts of Interest: The authors declare no conflicts of interest.

Funding: The Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education (NRF-2015R1D1A1A02061943).

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.esxm.2017.12.004.

eTable 1. Baseline serum levels of immunoglobulins and sexual hormones

Variables	Serum results	Reference range
Immunoglobulins (mg/dL)		
IgA	166	84–438
IgM	72	57–288
IgG	1,462	680–1,620
IgG1	802	382–929
IgG2	606	242–700
IgG3	19*	22–176
IgG4	28	3.9–86
Sexual hormones		
E_2 (pg/mL)	86.98*	0–39.8
Prolactin (ng/mL)	1.09*	2.1–17.7
Testosterone (ng/dL)	10.49*	241–827
LH (mIU/mL)	8.03	1.5–9.3
FSH (mIU/mL)	17.15	1.4–18.1

E_2 = estradiol; FSH = follicle-stimulating hormone; LH = luteinizing hormone.
*Values outside the normal range.

eTable 2. Changes in answers to questions from the MSHQ and IIEF

	Time		
Questionnaires	Before ILIT	8 mo after ILIT	15 mo after ILIT
MSHQ 2. In the past month, if you could get an erection without using drugs like Viagra, how often would you able to stay hard as long as you wanted to?	About half the time	Most of the time	Most of the time
MSHQ 9. In the past month, how would you rate the amount or volume of semen when you ejaculate?	A little less than it used to be	As much as it always was	As much as it always was
MSHQ 10. Compared with 1 mo ago, would you say the physical pleasure you feel when you ejaculate has …	Neither increased nor decreased	Increased moderately	Increased moderately
MSHQ 11. In the past month, have you experienced any physical pain or discomfort when you ejaculated? Would you say you have …	Extreme pain or discomfort	Moderate pain or discomfort	Slight pain or discomfort
MSHQ 12. In the past month, if you have had any ejaculation difficulties or have been unable to ejaculate, have you been bothered by this?	Very bothered	Moderately bothered	A little bit bothered
IIEF 12. How would you rate your level of sexual desire?	Low	Low	Moderate
IIEF 13. How satisfied have you been with your overall sex life?	Moderately dissatisfied	Moderately dissatisfied	Equally satisfied and dissatisfied

IIEF = International Index of Erectile Function; ILIT = intralymphatic immunotherapy; MSHQ = Male Sexual Health Questionnaire.

eTable 3. Semen analysis before and 8 months after ILIT

	Time	
	Before ILIT	8 mo after ILIT
Amount (mL)	1.0	1.5
Sperm, n	4,395	3,185
Sperm with normal motility, %	20	30
Sperm with normal morphology, %	30	40
pH	8.0	8.5
Micro RBC count/HPF	0∼1	0∼1
Micro WBC count/HPF	1∼3	0∼1

HPF = high-power field; ILIT = intralymphatic immunotherapy; RBC = red blood cell; WBC = white blood cell.

eTable 4. Skin prick test and intradermal test with autologous semen

	Skin prick test		Intradermal test	
	Semen/histamine ratio		Semen/saline ratio	
Dilution of semen	Before ILIT	8 mo after ILIT	Before ILIT	8 mo after ILIT
1/1 (undiluted)	0.58	0.46	Not done	Not done
1/4	0.33	0.38	Not done	Not done
1/40	0.33	0.31	1.06	1.81
1/400	0.33	0.46	1.00	1.50
1/4,000	0.17	0.38	0.94	1.75
1/40,000	0.17	0.23	0.72	1.31
1/400,000	0.00	0.23	0.56	1.50
1/4,000,000	0.00	0.31	0.50	1.38

ILIT = intralymphatic immunotherapy.